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EXAMINER	
ZAREK, PAUL E	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/595,935	MERCEP ET AL.	
	Examiner	Art Unit	
	Paul Zarek	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/19/2006, 11/21/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-15 have been amended by the Applicant in correspondence filed on 05/19/2006. Claims 1-15 are currently pending. This is the first Office Action on the merits of the claim(s).

Election/Restrictions

2. Applicant's election with traverse of Group I, drawn to a method of treating a disease, damage, or disorder of the central nervous system comprising administration of a compound of formula I wherein X is O in the reply filed on 11/21/2008 is acknowledged. Election with traverse of the species [3-(11-chloro-1,8-dioxa-dibenzo[e,h]azulen-2-ylmethoxy)-propyl]dimethyl-amine is also acknowledged The traversal is on the ground(s) that the art used to remove the special technical feature of the invention would be equally applicable to any of the groups and that the Examiner has not demonstrated why a restriction is proper. Applicants also allege that the basis of a requirement of restriction on substituent X is improper as substituent X has "nothing to do with the feature (the tetrahydro furan ring) which the Office alleges destroys Unity." Applicants further allege that the recited genus is already being examined in its entirety in copending application 10/515,678, therefore representing a "clear inconsistency in Office practice". This is not found persuasive because the substitution of one heteroatom for another in a ring system would not necessarily imbue the resultant compound with similar reactivity as the original compound. However, oxygen and sulfur are recognized bioisosteres, such that one of ordinary skill in the art would expect -O-, -S-, -S(=O)-, and $-S(=O)_2-$ would be obvious variants

of each other, and, hence the restriction between Groups I and II is vacated. Nitrogen, though, is not chemically equivalent to oxygen, sulfur, and S(=O) or $S(=O)_2$, are not chemically equivalent to each other. Therefore, the restriction between Groups I/II and III is maintained. That the basis of breaking Unity of Invention is inconsequential to the portion supposedly endowing Unity is not a valid argument. The claimed method was rendered obvious by the prior art, and, therefore, the inventions as claimed lack inventive step and, hence, a special technical feature. Finally, that an examiner of a similar copending application did not require a restriction and species election is not a valid argument. Each application is evaluated on its own merits.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-15 read on the elected species.

Priority

4. Applicant's claim for the benefit of a prior-filed international application PCT/HR04//00052 (filed on 11/19/2004) under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The effective filing date of the instant application is 11/19/2004.

5. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to patent application CROATIA P20030955A (filed on 11/21/2003). The date of foreign priority of the instant application is 11/21/2003.

Claim Objections

6. Claim 15 is objected to because of the following informalities: Claim 15 contains the limitation of "11-mhloro-2-methyl-1,8-dioxa-dibenzo[e,h]azulene" in line 5. Appropriate

correction is required. For art purposes, Examiner will interpret this as 11-chloro-2-methyl-1,8-dioxa-dibenzo[e,h]azulene.

Claim Rejections - 35 USC § 112 (1st paragraph)

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a disease, damage, or disorder of the central nervous system (CNS) comprising administration of a compound of formula (I) or pharmaceutically acceptable salt, thereof, does not reasonably provide enablement for method of treating a disease, damage, or disorder of the central nervous system (CNS) comprising administration of a solvate of a compound of formula (I) . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

9. *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-07, set forth eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (MPEP § 2164.01(a))

a. *The breadth of the claim*: The rejected claims are drawn to a method of treating a disease, damage, or disorder of the central nervous system (CNS) comprising administration of a compound of formula (I) or pharmaceutically acceptable salt or

solvate, thereof. Applicants do not limit what would constitute a solvate, so the claim reads on all pharmaceutically acceptable solvates;

b. *Nature of the invention*: The nature of the invention is a method of treating a disease, damage, or disorder of the central nervous system (CNS) comprising administration of a compound of formula (I) or pharmaceutically acceptable salt, thereof.;

c. *The state of the prior art*: Approximately one third of drugs are capable of forming crystalline hydrates (Vippagunta, et al., provided in IDS, section 3.1);

d. *Level of one of ordinary skill in the art*: One of ordinary skill in the art would be medicinal chemists, neuroscientists, or physicians investigating CNS disorders, diseases or damage. Such a level of skill would be considered high;

e. *Level of predictability in the art*: Just because many drugs are capable of forming hydrates or solvates does not mean that the resulting hydrate or solvate can be predicted before hand. Vippagunta, et al., teach that predicting the formation of solvates or hydrates of a compound is "complex and difficult." "There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates." pg 18, Section 3.4);

f. *Amount of direction provided by the inventor*: Applicants describe "pharmaceutically acceptable solvates" to be hydrates, ethanolates and similar (pg 17, paragraph 4);

g. *Existence of working examples*: Applicants allege to have tested several compounds for their ability to bind to 5-HT_A and 5-HT_{2C} receptors. Applicants to not disclose which compounds or solvates bind to these receptors; and,

h. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure*: Vippagunta, et al., is explicit in their statement that the formation of solvates or hydrates can not be known without experimentation. Indeed, one of ordinary skill in the art could not ascertain which solvates or hydrates would form with any reasonable expectation of success. The instant specification does not make up for this deficiency, as there is no guidance to an ordinarily skilled artisan to either make a solvate or hydrate of a compound of formula (I) or use said solvate/hydrate to treat anthrax or infections. Undue and unpredictable experimentation would be required to use the invention as claimed.

10. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administrating a compound of formula (I), or salt thereof) for the treatment of depression, bipolar disorders, addiction, anorexia, stroke, Alzheimer's disease, and Parkinson's disease, does not reasonably provide enablement for administrating a compound of formula (I), or salt thereof) for the treatment of any CNS-related disease, damage, or disorder not listed above, or prevention of any CNS-related disease, damage, or disorder (including those listed above). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The relevant Wands factors are discussed below.

a. *The breadth of the claim*: The rejected claims are drawn to a method of treating a disease, damage, or disorder of the central nervous system (CNS) comprising administration of a compound of formula (I) or pharmaceutically acceptable salt or solvate, thereof. The instant specification defines treatment to include preventing the

appearance of clinical symptoms of the CNS damage, disorder, or disease. This is tantamount to preventing the onset of the CNS damage, disorder, or disease, itself.

"Prevent," "prevention," and "prophylaxis" are potent terms implying that the method of prevention, or a prophylactic agent will necessarily prevent CNS disease, damage, or disorder in every subject that receives the compound at any point prior to what would have been the onset of the disease, damage, or disorder.

b. *Nature of the invention*: The nature of the invention is a method of treating depression, bipolar disorders, addiction, anorexia, stroke, Alzheimer's disease, and Parkinson's disease comprising administration of a compound of formula (I), or pharmaceutically acceptable salt, thereof;

c. *The state of the prior art*: The breadth of conditions encompassed by CNS disease, damage, and disorders, is exceedingly vast and includes numerous conditions that possess etiologies and symptoms that do not utilize identical or similar therapies. Most CNS diseases, damages, and disorders involve complex, multifaceted causes, including genetic and lifestyle causes.

The prior art teach that the compounds of formula (I) are TNF-α and IL-1 inhibitors (Mercep, et al., International Application No. WO 03/097649, abstract). Tobinick (US PreGrant Publication No. 2003/0049256) teaches that antagonists of TNF-α and IL-1 can treat various diseases and disorders of the CNS, including Alzheimer's disease, Parkinson's disease, bipolar disorder, schizophrenia, migraine, addiction, and stroke (abstract).

Given the diverse nature of causes of CNS diseases, damage, and disorders, it is impossible to prevent the onset of the diseases, damages, and disorders;

d. *Level of one of ordinary skill in the art*: see above;

e. *Level of predictability in the art*: The prior art clearly indicates TNF-α and IL-1 to be efficacious for some diseases and disorders, though certainly not all. The prior art also indicates that the compounds of the invention are known to be TNF-α and IL-1 inhibitors;

f. *Amount of direction provided by the inventor*: Applicants state that irregularities in the steady state of biogenic amines are a cause of various mental diseases (pg 1, paragraph 2), and that restoring the appropriate steady state of said amines would be an effective therapy (pg 1, paragraph 3). Applicants further disclose that 5-HT_A receptors are valid targets for treatment (pg 2, paragraph 1). Applicants disclose that tetracyclic antidepressants are used for treating CNS disorders and diseases. Applicants also disclose that the claimed tetracyclic compounds of formula (I) are TNF-α and IL-1 inhibitors;

g. *Existence of working examples*: Applicants demonstrate that the some of the claimed compounds are effective therapies in murine models of depression (forced swim test, tail suspension test, and the m-CPP test) and bipolar mania (amphetamine-induced hyperlocomotion test). The ATN-test is merely an *in vivo* screening assay demonstrating whether a specific compound binds to the dopamine, serotonin, and adrenergic receptors, which does not demonstrate therapeutic efficacy. Moreover, Applicants disclose that only some of the possible compounds were tested, and that some of the compounds tested

were not efficacious in all of the experiments. Applicants do not disclose which compounds were tested. No models of prevention are disclosed; and,

h. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure*: Applicants are claiming that the compounds of formula (I) are effective therapeutically and prophylactically against all CNS-related diseases, damages, and disorders. The instant specification provides enabling support for treatment of depression and bipolar disorders. The prior art provides enabling disclosure for Alzheimer's disease, Parkinson's disease, bipolar disorder, schizophrenia, migraine, addiction, and stroke. Neither the instant specification nor the prior art would enable one of ordinary skill in the art at the time the invention was made to treat a different CNS disorder, damage, or disorders, or prevent any disorders. To make and use the invention commensurate with the scope of the rejected claims, a skilled artisan would have to ignore the teachings of the art regarding the etiologies of the CNS diseases, damages, and disorders, and the fact that such diseases, damages, and disorders cannot be prevented. What is more, the instant application provides no guidance with regard to which compound(s) of formula (I) would be therapeutically effective against which CNS-related condition. Therefore, the instant specification does not fully enable the rejected claims.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having

ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mercep, et al. (International Application No. WO 01/087890, provided in IDS) in view of King (Medicinal Chemistry, 1994, provided in IDS), Müller and Ackenheil (Progress in Neuropsychopharmacology and Biological Psychiatry, 1998), and Tobinick (US Patent No. 6,471,961, 2002).

14. Claim 1 of the instant application is drawn to a method of treating a disease, damage, or disorder of the CNS associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter comprising administration of a compound of formula (I). Claim 2 limits the biogenic amine to serotonin, norepinephrine, or dopamine. Claim 3 limits the neurotransmitter to glutamate. Claims 4-9 limit the intended result of the compounds (i.e. binds to the receptor of a biogenic amine). Claims 10 and 11 limit the disease or disorder (Claim 10) or damage (Claim 11). Claims 12-15 limit the substituents of the compound of formula (I). The elected species [3-(11-chloro-1,8-dioxa-dibenzo[e,h]azulen-2-ylmethoxy)-propyl]dimethyl-amine reads on all of the claims, and is specifically listed in Claim 15.

15. Mercep, et al., teach the compound [3-(11-chloro-8-oxa-1-thia-dibenzo[e,h]azulen-2-ylmethoxy)-propyl]dimethyl-amine (Example 11) as an inhibitor of TNF-α and IL-1. The compound taught by Mercep, et al., differs from the elected species only in that the furan of the elected species is replaced by a thiophene in the prior art. King teaches that -S- and -O- are bioisosteres (Table 1), such that one of ordinary skill in the art would reasonably expect that the two compounds would behave in a similar fashion (e.g. the elected species would be an inhibitor of TNF-α and IL-1, like the compound taught by Mercep, et al.), absent evidence to the contrary. Mercep, et al., and King do not teach the elected species for the treatment of CNS diseases, damages, or disorders.

16. Müller and Ackenheil teach that IL-1 and TNF-α play important roles in the etiology of CNS diseases and disorders. IL-1 has been shown to induce psychomotor retardation, fever, sleep disturbance, and anorexia (pg 6, paragraph 6). IL-1 has also been shown to increase noradrenaline, serotonin, and dopamine turnover (pg 9, paragraph 2). TNF-α also influences neurotransmitter balance, and its effects on the catecholaminergic system "shows parallels to the pathophysiologicial mechanisms discussed for schizophrenia" (pg 10, paragraph 3).

17. Tobinick teaches that antagonists (aka inhibitors) of IL-1 can suppress inflammation which is important for the development of neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases (col 1, lines 63-67). Inhibiting IL-1, then, would be an effective treatment for neurodegenerative disorders.

18. Many of the CNS-related diseases, disorders, and damages are caused, in part, by a defect in neurochemical equilibrium within the CNS. Major neurotransmitters include serotonin, dopamine, norepinephrine, and glutamate. Limiting CNS-related disorders to those that include

a nonequilibrium in a neurotransmitter is not considered to be a patently distinguishing feature as the vast majority, if not all, of the CNS-related diseases, disorders, and damages would be encompassed by this. Thus, Mercep, et al., reads on Claims 2 and 3.

19. Claims 4-9 contain wherein clauses indicating the intended result of the method of treatment (e.g. binding to the receptor of a biogenic amine). Such an intended result is not considered to be a patently distinguishing feature as any compound that reads on Claim 1 would also have the intended result of Claims 4-9. A "whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005).

20. Taken together, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to incorporate the teachings of Mercep, et al., King, Müller and Ackenheil, and Tobinick to treat CNS diseases, damages, and disorders with the elected species.

21. Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrés-Gil, et al. (International Application No. WO 99/19317, provided in IDS).

22. Claims 1-14 are described above.

23. Andrés-Gil, et al., teach tetracylic tetrahydrofuran derivatives as therapies for various CNS-related disease, disorders, and damage, including depression, bipolar disorder, schizophrenia, migraine, addiction, stroke, and neurodegenerative diseases (which include Alzheimer's disease and Parkinson's disease) (pg 9, lines 21-30, and pg 10, lines 1-5). The compound of formula (I) taught by Andrés-Gil, et al., is substantially similar to compound of formula (I) disclosed in the instant claims. The major difference being that the compound taught

by Andrés-Gil, et a., possess a fully saturated furan ring, whereas the instant application disclose an unsaturated furan ring. A specific embodiment (Table 2, Cmpd 24) of Andrés-Gil, et al., comprises the same substituents of an embodiment of the instant invention where X is O, Y is H, Z is a halogen, and R^1 is C_1 alkyl substituted with a dimethylamino group. The compounds are so similar that one of ordinary skill would reasonably expect that they would behave similarly (e.g. to treat CNS-related diseases, disorders, or damages), in the absence of unexpected results.

24. Many of the CNS-related diseases, disorders, and damages are caused, in part, by a defect in neurochemical equilibrium within the CNS. Major neurotransmitters include serotonin, dopamine, norepinephrine, and glutamate. Limiting CNS-related disorders to those that include a nonequilibrium in a neurotransmitter is not considered to be a patently distinguishing feature as the vast majority, if not all, of the CNS-related diseases, disorders, and damages would be encompassed by this. Thus, Andrés-Gil, et al., reads on Claims 2 and 3.

25. Claims 4-9 contain wherein clauses indicating the intended result of the method of treatment (e.g. binding to the receptor of a biogenic amine). Such an intended result is not considered to be a patently distinguishing feature as any compound that reads on Claim 1 would also have the intended result of Claims 4-9. A "whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005).

26. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Andrés-Gil, et al. (above) as applied to claims 1-14 above, and further in view of King (above).

27. Claim 15 is described above.

28. Andrés-Gil, et al., teach numerous compounds that are effective for the treatment of CNS diseases, damages, and disorders, but do not disclose the elected species or any compound listed in Claim 15. Andrés-Gil, et al., however, do disclose that R^1 can be a up to 6 carbons long. King teaches that –O- and $–CH_2-$ are bioisosteres, and therefore have similar pharmacological activity, in the absence of unexpected results. Thus, one of ordinary skill in the art would reasonably expect that the elected species of the instant application would behave in a similar fashion as the compound taught by Andrés-Gil, et al. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the compounds of formula (I) listed in Claim 15 for the treatment of CNS diseases, disorders, and damages.

Conclusion

29. Claims 1-15 are rejected.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Zarek whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/Rita J. Desai/
Primary Examiner, Art Unit 1625